0022-5347/05/1735-1482/0
THE JOURNAL OF UROLOGY®

Vol. 173, 1482–1486, May 2005
Printed in U.S.A.
DOI: 10.1097/01.ju.0000154629.45832.30

EVALUATION AND MANAGEMENT OF RENAL TUMORS IN THE BIRT-HOGG-DUBÉ SYNDROME

CHRISTIAN P. PAVLOVICH,* ROBERT L. GRUBB, III,* KATHLEEN HURLEY, GLADYS M. GLENN, JORGE TORO, LAURA S. SCHMIDT, CARLOS TORRES-CABALA, MARIA J. MERINO, BERTON ZBAR, PETER CHOYKE, MCCLELLAN M. WALTHER AND W. MARSTON LINEHAN†

From the Urologic Oncology (CP, RLG III, KH, MMW, MWL) and Genetic Epidemiology (GMG, JT) Branches, Division of Cancer Epidemiology and Genetics, National Cancer Institute and Basic Research Program, SAIC-Frederick, Inc., National Cancer Institute Frederick (LSS), Frederick and Laboratories of Pathology (CT-C, MJM) and Immunobiology (BZ) and Molecular Imaging Program (PC), Center for Cancer Research, Bethesda, Maryland

ABSTRACT

Purpose: Herein we describe the evaluation and management of renal tumors in Birt-Hogg-Dubé (BHD), an autosomal dominant disorder predisposing to cutaneous fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax and renal tumors.

Materials and Methods: A total of 124 affected individuals underwent comprehensive clinical evaluation, including body computerized tomography, to determine cutaneous, pulmonary and renal manifestations of BHD. Of these individuals 14 had their renal tumors managed at our institution.

Results: Of the 124 BHD affected individuals 34 (27%) had renal tumors of various histologies, most commonly hybrid oncocytic tumor and chromophobe renal carcinoma. Average age at renal tumor detection was 50.4 years and multiple tumors were found in a majority of patients. Some patients with renal tumors were identified that did not have the characteristic cutaneous hallmarks of BHD. In 4 of the 14 patients treated at our institution small (less than 3 cm) renal tumors were observed, while 10 others underwent a total of 12 renal procedures, including 4 radical and 8 partial nephrectomies. At a median of 38 months of followup 5 of these 10 patients remained free of disease, 3 had small renal tumors and 2 died of metastatic renal cancer.

Conclusions: Patients with BHD are at risk for multiple renal tumors that are often malignant and can metastasize. Individuals at risk or affected by BHD should be radiographically screened for renal tumors at periodic intervals and they are best treated with nephron sparing surgical approaches. Genetic testing for this syndrome is now available.

KEY WORDS: kidney, kidney neoplasms, gene expression, pneumothorax

Birt-Hogg-Dubé (BHD), which was described in 1977,[1] is now known to be an autosomal dominant, inherited cancer syndrome of unknown incidence, in which affected individuals may have benign cutaneous tumors or fibrofolliculomas, pulmonary air filled cysts and spontaneous pneumothorax, and renal neoplasms (figs. 1 to 3). Fibrofolliculomas tend to appear in the third or fourth decade of life as small white or skin-colored papules on the face, neck, back and upper trunk. These cutaneous lesions may progress with time and they are primarily of diagnostic and cosmetic consequence. In 1993 a patient with BHD was reported to have bilateral renal cell carcinomas (RCCs)[2] and by 1999 the familial nature of the kidney tumors was described and characterized in a study of 3 unrelated BHD kindred.[3] The *BHD* gene was mapped to chromosome 17p11.2[4] and further study of BHD kindred led to identification of the *BHD* gene.[5] *BHD* encodes a novel protein named folliculin, of unknown function.[5] Germline mutations in *BHD* generally cause protein truncations but the exact role of *BHD* in the resultant phenotypic abnormalities remains to be determined. Germline mutation testing in individuals at risk can determine whether they carry a mutation in the *BHD* gene and are at increased risk for renal cancer.[5]

von Hippel-Lindau and hereditary papillary RCC are hereditary cancer syndromes associated with specific histological types of renal cell carcinoma, namely clear cell and type I papillary RCC, respectively.[6] In marked contrast, BHD predisposes to various renal tumor histological types.[7] In the current study we update our description of the renal manifestations of BHD and describe our current renal tumor management strategy. Because BHD, like other hereditary renal tumor syndromes, may predispose to multiple kidney tumors, we used nephron sparing approaches when possible because of the lifelong risk of subsequent renal tumors in affected patients.[8]

MATERIALS AND METHODS

Families at risk for BHD and individuals with a history of familial renal tumors were initially screened at the National Cancer Institute (NCI) during the study period of 1996 to 2001.[3–5,9] They were followed through April 2004. Family members were enrolled in a screening, treatment and genetic diagnosis protocol approved by the institutional review board. Medical histories, including pathological reports and tumor tissues, were obtained. Physical examinations and

Submitted for publication August 12, 2004.
Study received institutional review board approval.
The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the United States Government.
Supported with Federal funds from the National Cancer Institute, National Institutes of Health under Contract N01-C0–12400.
* Equal study contribution.
† Correspondence: Urologic Oncology Branch, Building 10, Room 2B47, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland 20892-1501 (telephone: 301-496-6353; FAX: 301-402-0922; e-mail: UOB@nih.gov).

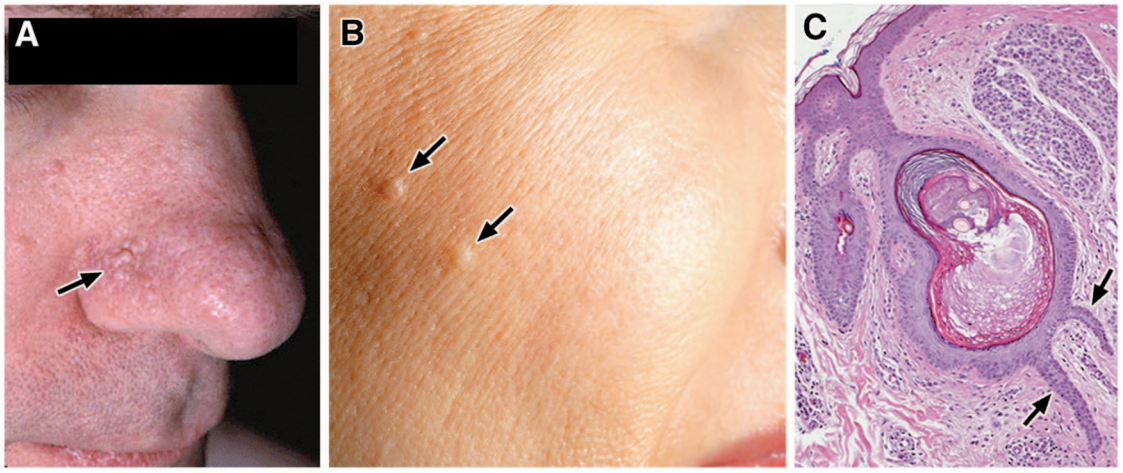

FIG. 1. BHD cutaneous manifestations. BHD hallmark is cutaneous fibrofolliculoma (*A* and *B*, arrows). Fibrofolliculoma is benign tumor of hair follicle that can appear on face and upper trunk. Histologically fibrofolliculomas show epithelial strands emanating from central hair follicle (*C*, arrow). Reduced from ×150.

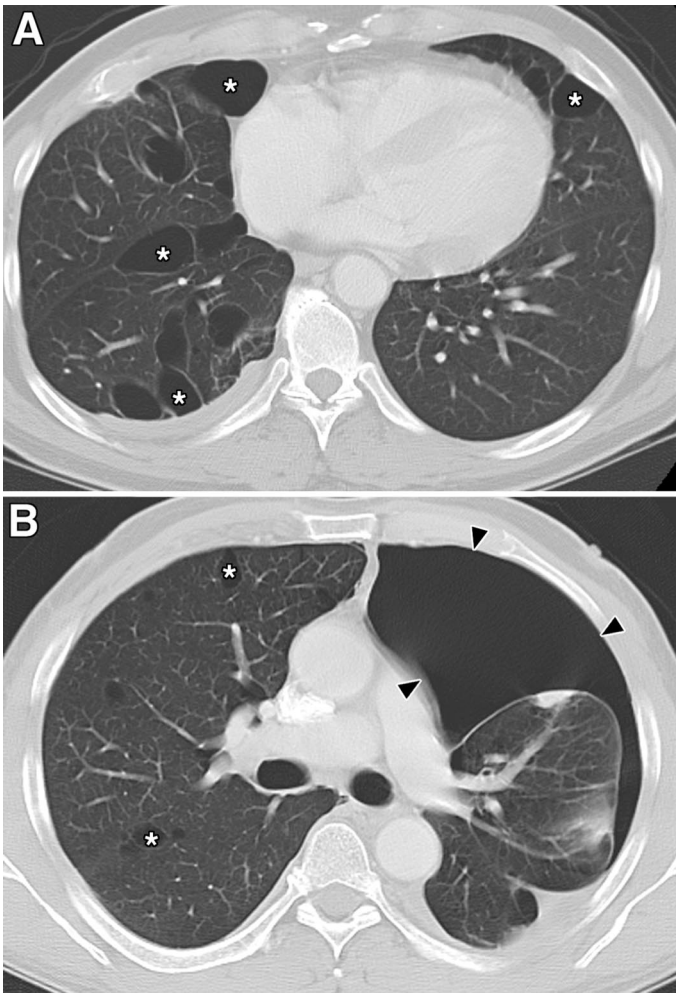

FIG. 2. Pulmonary manifestations of BHD. Patients with BHD are at risk for lung cysts (*A* and *B*, asterisks) and spontaneous pneumothorax (*B*, arrowheads).

dermatological screening, including cutaneous biopsies, were performed in family members who were 20 years or older. A family was considered affected by BHD when at least 1 member was found to have a histologically confirmed fibrofolliculoma (often greater than 10 were found clinically) and/or a germline mutation of the *BHD* gene. The presence of skin lesions characteristic of fibrofolliculoma was the primary clinical diagnostic criterion for BHD (fig. 1). Patients without cutaneous lesions were also considered to have BHD if they were obligate carriers of the *BHD* gene, were found to have a germline *BHD* gene mutation[5] or were inheritors of the BHD affected haplotype.

Patients evaluated at NCI underwent pre-contrast and post-contrast medium computerized tomography of the chest, abdomen and pelvis after providing informed consent. Only predominantly solid renal lesions greater than 1 cm that enhanced more than 20 HU were considered renal tumors.

In general surgery was recommended to patients when at least 1 tumor became greater than 3 cm in diameter and surgery or close observation was recommended for smaller tumors. The operations performed were partial or radical nephrectomy, the latter for central tumors greater than T2. When possible, all solid lesions in the ipsilateral kidney were surgically resected. Intraoperative ultrasound was used to identify small lesions that may not have been seen on preoperative imaging or that were not visible or palpable during the operation.[10] Patients initially treated elsewhere were considered affected by renal neoplasms if confirmatory pathological reports or materials pertaining to the original surgery were available for review.

Tumors were classified according to the 1997 Heidelberg and Rochester classifications of renal tumors.[11,12] Hybrid oncocytic tumor, a recently described form of renal carcinoma that combines elements of oncocytoma and chromophobe renal cell carcinoma, was also used in the classification system (fig. 4).[7,13]

RESULTS

Clinical evaluation. Individuals from 45 BHD families were screened during the study interval. The phenotypic, pathological and genetic characteristics of some of these families have been reported previously.[3–5,9] From these families 124 individuals were screened at NCI and diagnosed with BHD. Evaluation of these families and their pedigrees demonstrated the diverse clinical manifestations of BHD between and within affected families, and illustrate the autosomal dominant inheritance of the cutaneous, pulmonary and renal manifestations of the syndrome (figs. 1 to 3 and 5).

Screening for renal tumors. Of the 124 BHD affected individuals screened for renal tumors 18 had a prior history of renal neoplasms. Abdominal imaging yielded an additional 16 patients with renal tumors of the remaining 106 (15%), resulting in renal tumors in a total of 34 individuals with BHD (18 + 16 = 34 and 34/124 = 27.4%). There were 25

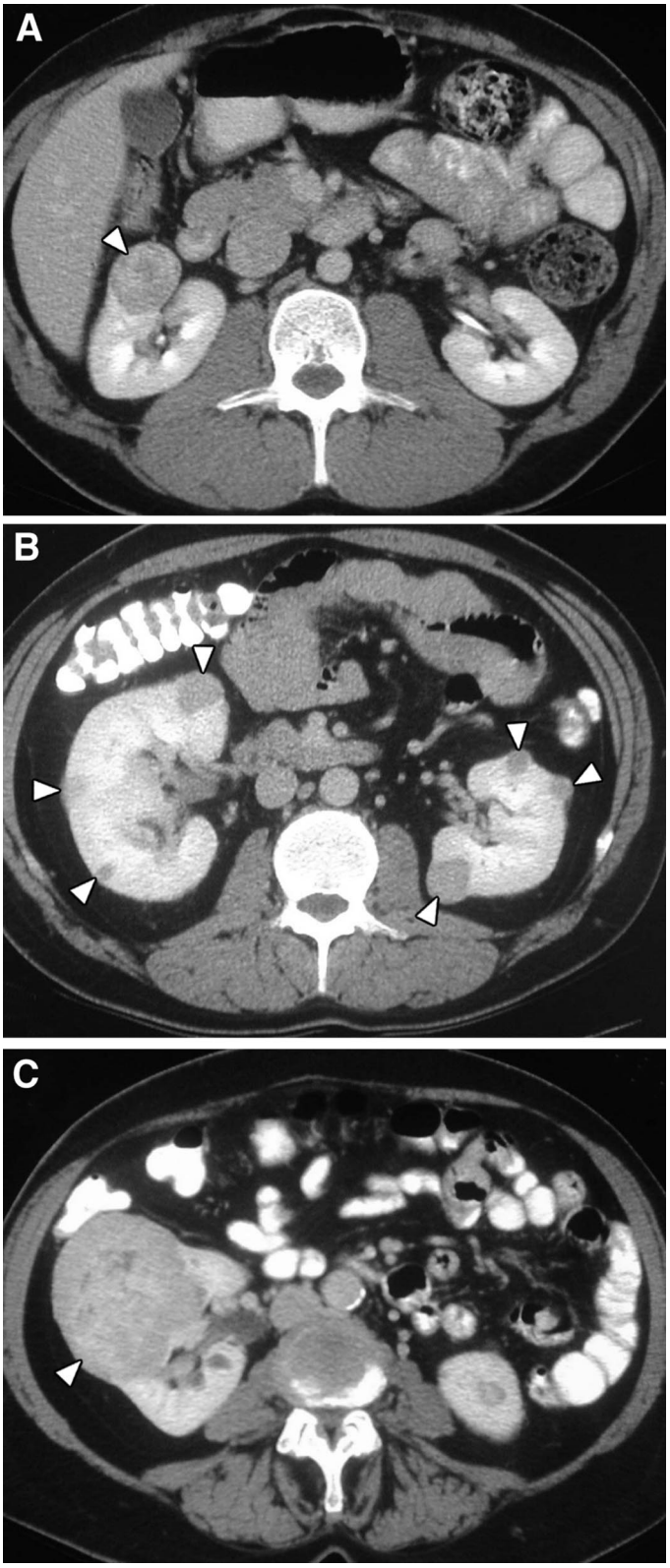

FIG. 3. BHD associated renal tumors can be solitary (*A*, arrowhead) or multifocal and bilateral (*B*, arrowheads). BHD renal tumors are often malignant. They can grow (*C*, arrowhead) and metastasize.

males (74%) and 9 females (26%) affected by renal neoplasms with an average age of 50.4 years (range 31 to 74) (table 1). Renal tumors were multifocal in 22 of 34 cases (65%), often involved the 2 kidneys and were solid and not cystic or even partly cystic in nature. Conversely just more than half of the BHD families (23 or 45 families or 51 individuals screened) had no members in whom renal tumors were detected by abdominal computerized tomography.

BHD kindred with no detectable cutaneous manifestations. During this study we screened 11 members of a kidney cancer family referred to NCI for evaluation. Of the 11 individuals 3 sisters had previously been found to have renal cancer. Two of the sisters had each undergone radical and partial nephrectomy for renal cell carcinoma. The third sister had undergone radical nephrectomy. Pathological results of the renal tumors of the sisters was remarkably similar, in that all were the hybrid oncocytic histological type. When individuals from this kindred were screened, pulmonary cysts were found in 8 of 11 family members, including the 3 sisters with kidney cancer. Careful dermatological evaluation of family members failed to reveal cutaneous fibrofolliculomas. Germline mutation testing for alteration of the *BHD* gene was performed in an affected relative from this kindred, as described by Nickerson et al,[5] and *BHD* mutation was found in that individual (L. Schmidt, personal communication). Although it is certainly possible that fibrofolliculomas could appear later in life in affected individuals, this kindred illustrates why clinicians should consider the diagnosis of BHD in patients with chromophobe/oncocytic renal neoplasms even in the absence of cutaneous lesions of BHD.

Management of BHD associated renal tumors. In 14 patients with BHD the tumors were managed at NCI. Four individuals had small (less than 3 cm) tumors that were observed. In the 10 patients who underwent surgery at NCI partial nephrectomy was performed on 8 kidneys using a previously described technique[14] and 4 kidneys were removed by radical nephrectomy. Median followup in these 10 patients was 38 months (range 2 to 72), during which time 3 had detectable renal tumor recurrences. One patient had detectable tumors in a previously operated kidney and 2 had detectable tumors in the nonoperated kidney. The largest of these tumors was 2 cm.

Of the 10 patients 2 died of metastatic disease after radical nephrectomy. One underwent bilateral nephrectomies for multiple tumors and received a kidney transplant. Pathological examination revealed that his largest tumor was an 8 cm clear cell RCC (pT2NxMx) with other smaller tumors of multiple histologies. This patient had biopsy proven paraspinal metastasis (clear cell histology) 56 months after his initial surgery and he died of disease shortly thereafter. The other patient had an 8 cm tumor with invasion of the perinephric fat and benign lymph nodes (pT3N0Mx), which was histologically shown to be predominantly clear cell (RCC) with areas of tubular papillary and chromophobe histology. This patient had biopsy proven retroperitoneal recurrence 5 months after surgery. Cytology was consistent with a clear cell origin. Despite receiving systemic immunotherapy, he eventually had osseous metastases and died 20 months postoperatively. No other patients have had metastatic disease to date.

Renal tumor pathology. In patients who underwent surgery at NCI an average of 7 tumors per renal unit were removed at surgery (median 5, range 1 to 22) (table 1). This number likely represents an underestimate of the number of tumors because in some cases, such as the 4 radical nephrectomies, there were too many small tumors to count accurately. The tumors were of various histologies, including primarily hybrid oncocytic tumors in 67%, chromophobe RCC in 23% and clear cell RCC in 7%, as previously described (table 2).[7] Tumor stage was pT1 to pT3N0 (table 1). Tumors of different histological types were found in the same patient in 4 of 10 patients (40%). Tumor histology was not clearly concordant within affected families. Microscopic lesions consistent with renal oncocytosis were noted in the parenchyma neighboring the macroscopic tumors in 6 of 7 cases (86%) in which there was evaluable tissue more than 5 mm from grossly neoplastic tumor.[7]

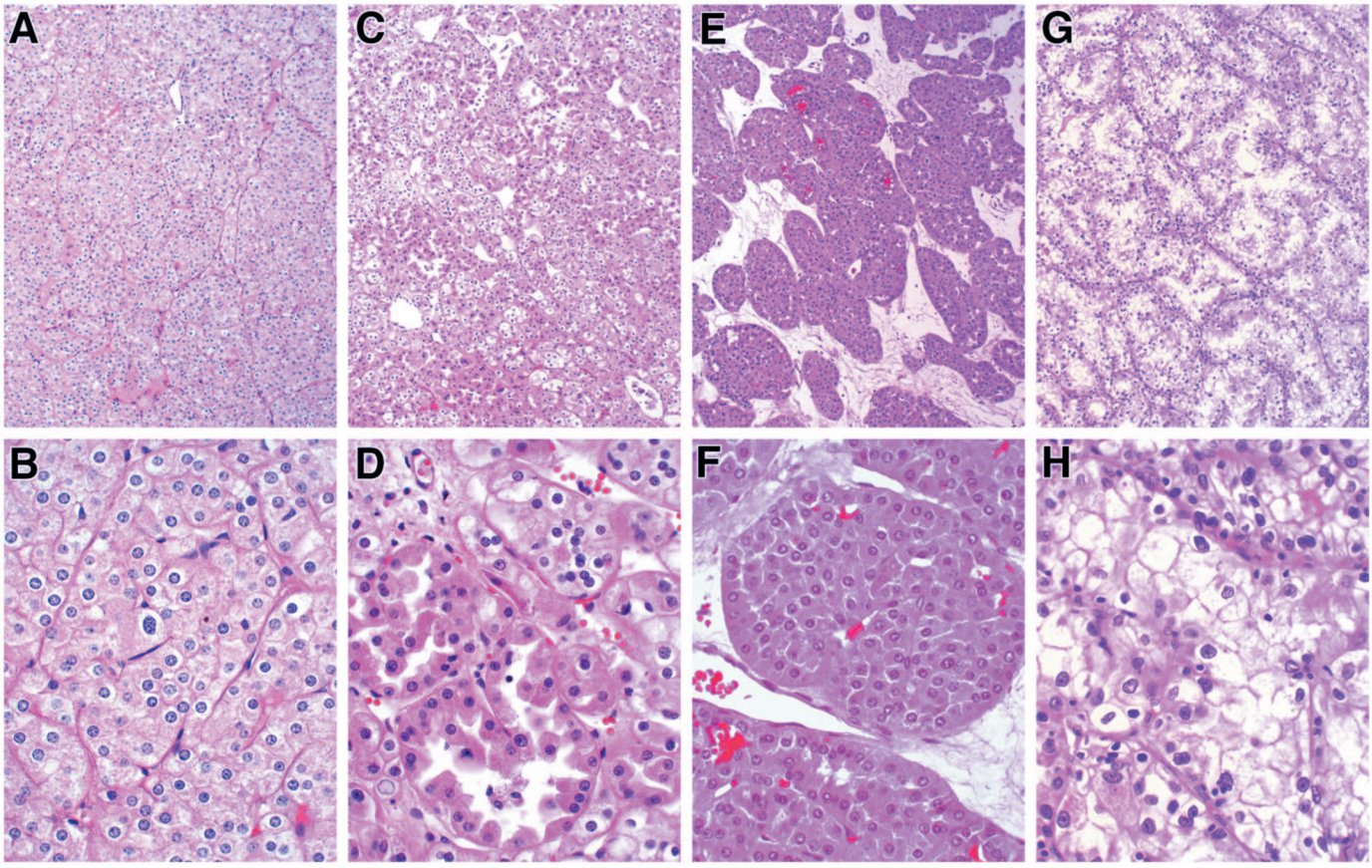

FIG. 4. BHD renal pathology. BHD associated renal tumors can be chromophobe (*A* and *B*), hybrid oncocytic tumors (*C* and *D*), oncocytoma (*E* and *F*) or clear cell renal carcinoma (*G*). Multiple histological types of RCC can be found in same BHD family, in same patient or even in same kidney. Reduced from ×100 (*A*, *C*, *E* and *G*) and ×400 (*B*, *D*, *F* and *H*).

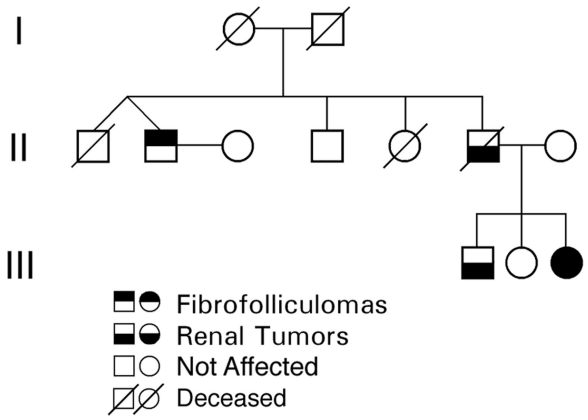

FIG. 5. Representative BHD pedigree. BHD is hereditary cancer syndrome that is inherited in autosomal dominant fashion. Affected individuals are at risk for cutaneous fibrofolliculoma, pulmonary cysts, spontaneous pneumothorax and renal tumors.

TABLE 1. *Patient and tumor characteristics*

No. pts	34	
No. men (%)	25	(74)
No. women (%)	9	(26)
Mean age (range)	50.4	(31–74)
No. multiple tumors (%)	22	(65)
No. bilat involvement (%)	19	(56)
Mean No. tumors/renal unit (range)	7	(1–22)
No. pathological stage (%):		
pT1	17	(50)
pT2	8	(23)
pT3	5	(15)
No. less than 3 cm ongoing observation (%)	4	(12)

TABLE 2. *Histological characteristics of tumors resected at NCI*

Tumor Histology	No. Pts (%)
Overall	84
Hybrid oncocytic	56 (67)
Chromophobe	19 (23)
Clear cell	6 (7)
Oncocytoma	3 (3)

DISCUSSION

BHD is an autosomal dominant disorder of which the hallmark lesions are fibrofolliculomas, namely benign tumors of the hair follicle that appear in the third to fourth decade of life as papules on the face, neck, back and trunk. Subsequent studies revealed that individuals affected by BHD are at risk for renal tumors[2,3] as well as pulmonary cysts and spontaneous pneumothorax.[15] In the current study we found that more than 25% of patients with BHD had renal tumors, that is 34 of 124 (27.2%) with BHD evaluated at the NCI urological oncology clinic from 1996 to 2001 had renal neoplasms. This percent of patients affected with renal cancer is in contrast to a renal tumor prevalence of 15% in individuals with cutaneous BHD manifestations (fibrofolliculomas) who were recruited to NCI via mass mailings to North American dermatologists.[9] Either value (15% or 27.2%) is high compared with the prevalence of solid renal tumors in screened adult populations in Japan and the United States, which was found to be 0.09% and 0.2% respectively.[16,17]

The predominant renal tumor associated with BHD syn-

drome is hybrid oncocytic renal cell carcinoma, which contains a mixture of oncocytes and chromophobe cells (fig. 4, *C* and *D*).[7,13] Renal oncocytosis, that is small nodules of cells similar to those found in the larger hybrid tumors but scattered throughout the renal parenchyma, has been found in a majority of patients with BHD who underwent surgery, which suggests that the entire renal parenchyma in patients with BHD may be at increased risk for neoplasm.[7] In these patients each cell in the renal parenchyma carries an inherited germline *BHD* mutation, while inactivation of the remaining *BHD* allele by a "second (somatic) hit" has been shown, supporting a tumor suppressor role for *BHD*.[18] It is not known why a range of kidney cancer types occurs in patients with BHD. The finding that patients with BHD have distinctly different histological types of renal malignancies might indicate that tumors such as oncocytoma, hybrid-oncocytic RCC and chromophobe RCC represent a spectrum of the same disease.

To our knowledge the malignant nature of BHD associated renal tumors has not been previously established. In our experience BHD associated kidney cancer has the potential to be a lethal disease based on family histories of death from metastatic RCC in several patients with BHD. Two patients who underwent surgery at NCI subsequently died of metachronous metastatic disease. Each patient had large tumors with clear cell features and biopsies proved that the primary tumor was clear cell RCC. Our limited experience suggests that BHD associated chromophobe and hybrid oncocytic RCC may be of lesser malignant potential than BHD associated clear cell RCC but these lesions cannot be considered completely benign based on their cytomorphology and the known occasionally malignant behavior of chromophobe tumors.

In families in which multiple members are found to have chromophobe or hybrid oncocytic renal carcinomas BHD should be considered. Individuals with multifocal chromophobe or hybrid oncocytic renal carcinoma, or those with such tumor(s) and pulmonary cysts/spontaneous pneumothorax should also be screened for BHD. In addition, as we observed in the current study, some patients who do not have apparent cutaneous manifestations of BHD may still have the genetic syndrome absent fibrofolliculomas or they may appear later in life in these patients. Thus, when there is doubt about the diagnosis in a patient or family, germline mutation testing can solidify the diagnosis of BHD in individuals at risk.[5] Efforts are currently underway to determine why some *BHD* families have kidney cancer and others do not.

Urological surgeons who treat patients with BHD should keep in mind the potential for perioperative pneumothorax in these patients. A high percent of patients with BHD are affected with pulmonary cysts (almost 90%) and more than 20% have a history of spontaneous pneumothorax.[9] In at least 1 case postoperative pneumothorax unrelated to surgery occurred in a patient with BHD, which was managed by postoperative chest tube insertion.

CONCLUSIONS

BHD is an autosomal dominant hereditary cancer syndrome, in which affected individuals are at risk for cutaneous fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax and kidney tumors. Almost 30% of affected patients with BHD examined at our institution had solid renal tumors. Because of the spectrum of renal tumor histologies found in patients with BHD, their variable natural history and the risk of recurrent renal tumors in such patients, it is important for urologists to be aware of this syndrome. The identification of the *BHD* gene has made it possible in many cases to determine by genetic testing those affected by this syndrome. Periodic radiographic screening of at risk or affected patients with BHD for renal tumors is recommended starting in the fourth decade of life. Our current management approach for BHD associated renal tumors is to perform nephron sparing surgery when possible.

Rick Dreyfuss, Medical Arts and Photography Branch, National Institutes of Health assisted with figure preparation.

REFERENCES

1. Birt, A. R., Hogg, G. R., and Dube, W. J.: Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch Dermatol, **113:** 1674, 1977
2. Roth, J. S., Rabinowitz, A. D., Benson, M., and Grossman, M. E.: Bilateral renal cell carcinoma in the Birt-Hogg-Dube syndrome. J Am Acad Dermatol, **29:** 1055, 1993
3. Toro, J. R., Glenn, G., Duray, P., Darling, T., Weirich, G., Zbar, B. et al: Birt-Hogg-Dube syndrome: a novel marker of kidney neoplasia. Arch Dermatol, **135:** 1195, 1999
4. Schmidt, L. S., Warren, M. B., Nickerson, M. L., Weirich, G., Matrosova, V., Toro, J. R. et al: Birt-Hogg-Dubé syndrome, a genodermatosis associated with spontaneous pneumothorax and kidney neoplasia, maps to chromosome 17p11.2. Am J Hum Genet, **69:** 876, 2001
5. Nickerson, M. L., Warren, M. B., Toro, J. R., Matrosova, V., Glenn, G., Turner, M. L. et al: Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dube syndrome. Cancer Cell, **2:** 157, 2002
6. Linehan, W. M.: Editorial: kidney cancer—a unique opportunity for the development of disease specific therapy. J Urol, **168:** 2411, 2002
7. Pavlovich, C. P., Walther, M. M., Eyler, R. A., Hewitt, S. M., Zbar, B., Linehan, W. M. et al: Renal tumors in the Birt-Hogg-Dube syndrome. Am J Surg Pathol, **26:** 1542, 2002
8. Herring, J. C., Enquist, E. G., Chernoff, A., Linehan, W. M., Choyke, P. L., and Walther, M. M.: Parenchymal sparing surgery in patients with hereditary renal cell carcinoma: 10-year experience. J Urol, **165:** 777, 2001
9. Zbar, B., Alvord, W. G., Glenn, G., Turner, M., Pavlovich, C. P., Schmidt, L. et al: Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dube syndrome. Cancer Epidemiol Biomarkers Prev, **11:** 393, 2002
10. Choyke, P. L., Pavlovich, C. P., Daryanani, K. D., Hewitt, S. M., Linehan, W. M., and Walther, M. M.: Intraoperative ultrasound during renal parenchymal sparing surgery for hereditary renal cancers: a 10-year experience. J Urol, **165:** 397, 2001
11. Kovacs, G., Akhtar, M., Beckwith, B. J., Bugert, P., Cooper, C. S., Delahunt, B. et al: The Heidelberg classification of renal cell tumours. J Pathol, **183:** 131, 1997
12. Storkel, S., Eble, J. N., Adlakha, K., Amin, M., Blute, M. L., Bostwick, D. G. et al: Classification of renal cell carcinoma: Workgroup No. 1. Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer, **80:** 987, 1997
13. Tickoo, S. K., Reuter, V. E., Amin, M. B., Srigley, J. R., Epstein, J. I., Min, K. W. et al: Renal oncocytosis: a morphologic study of fourteen cases. Am J Surg Pathol, **23:** 1094, 1999
14. Walther, M. M., Thompson, N., and Linehan, W.: Enucleation procedures in patients with multiple hereditary renal tumors. World J Urol, **13:** 248, 1995
15. Binet, O., Robin, J., Vicart, M., Ventura, G., and Beltzer-Garelly, E. Fibromes perifolliculaires, polypose coliqe familiale, pneumothorax spontanes familiaux. Ann Dermatol Venereol, **113:** 928, 1986
16. Mihara, S., Kuroda, K., Yoshioka, R., and Koyama, W.: Early detection of renal cell carcinoma by ultrasonographic screening—based on the results of 13 years screening in Japan. Ultrasound Med Biol, **25:** 1033, 1999
17. Mitchell, T. L., Pippin, J. J., Devers, S. M., Kimball, T. E., Gibbons, L. W., Cooper, L. L. et al: Incidental detection of preclinical renal tumors with electron beam computed tomography: report of 26 consecutive operated patients. J Comput Assist Tomogr, **24:** 843, 2000
18. Khoo, S. K., Giraud, S., Kahnoski, K., Chen, J., Motorna, O., Nickolov, R. et al: Clinical and genetic studies of Birt-Hogg-Dube syndrome. J Med Genet, **39:** 906, 2002